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### Living kidney donor safety

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## Chapter five

# Nephrectomy elicits impact of age and BMI on renal hemodynamics: lower post-donation reserve capacity in older or overweight kidney donors

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## Abstract

Renal functional reserve could be relevant for maintenance of renal function after kidney donation. Older age and higher body mass index (BMI) may be associated with reduced reserve capacity (RC). We therefore investigated RC in 178 consecutive living kidney donors (39% male, age  $48 \pm 11$  years, BMI  $25.5 \pm 4.1$ ). RC was determined as the rise in glomerular filtration rate (GFR;  $^{125}\text{I}$ -iothalamate) after constant infusion of low-dose dopamine, 4 months before and 2 months after donor nephrectomy.

Before donor nephrectomy, GFR was  $114 \pm 20$  ml/min, with a reduction to  $72 \pm 12$  ml/min after donor nephrectomy. The dopamine-induced rise in GFR of  $11 \pm 10\%$  was reduced to  $5 \pm 7\%$  after donor nephrectomy ( $p \leq 0.001$ ). Before donor nephrectomy, older age and higher BMI did not affect reserve capacity. After donor nephrectomy, the response of GFR to dopamine independently and negatively correlated with older age and higher BMI. Moreover, post-donation reserve capacity was absent in obese donors. Presence of overweight had more impact on loss of RC in younger donors.

In conclusion, donor nephrectomy unmasked an age- and overweight-induced loss of reserve capacity. Possibly, donors with advanced age and/or overweight address their renal reserve to maintain renal function.

## Introduction

The kidney has a substantial functional reserve capacity that is assumed to be relevant for preservation of renal function after loss of functional renal mass, for instance after living kidney donation. Renal reserve capacity can be estimated from the renal hemodynamic response to intravenous administration of low-dose dopamine, an amino-acid solution or an oral protein load [1-3]. Dopamine induces vasodilation of predominantly the post-glomerular arteriole. The rise in GFR is allowed by concomitant dilation of the afferent arteriole, thus leading to a rise in glomerular perfusion and filtration. The resulting increase in glomerular filtration rate (GFR) is considered to be a reflection of renal reserve capacity [4].

Older age, by loss of nephrons and/or renal arteriosclerosis, has been associated with reduced renal reserve capacity [5-7]. In presence of hypertension, obese patients were also reported to have reduced renal reserve capacity, compared to lean hypertensive subjects [8], possibly due to hyperfiltration. In chronic renal disease, reserve capacity has been reported to be decreased, possibly due to hyperfiltration in the remaining nephrons [4]. However, data are not consistent, which may be due to relatively small study populations and differences in patient selection [9,10]. In a large series of 125 prospective living kidney donors (mean age  $49 \pm 11$  years; mean BMI  $25 \pm 4$  kg/m<sup>2</sup>), we did not find renal reserve capacity to be reduced in older or more overweight donors during pre-donation screening, presumably because kidney donors represent a healthy subset of the population. However, higher age and higher BMI were independently associated with a larger decrease in renal function early after donation, suggesting impairment in renal adaptive capacity. This had not been detected from the renal

hemodynamic responses to dopamine and amino acids prior to donation [11].

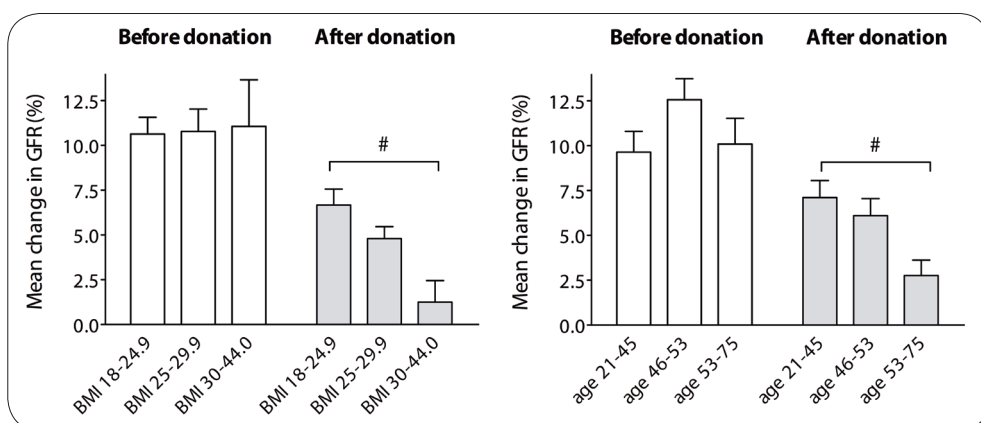
Effects of age and overweight on renal risk after living kidney donation are of clinical relevance, as –due to persistent donor shortage– older and/or overweight subjects are increasingly accepted for kidney donation. This implies that the long-term renal risk profile for the current donor population may not be similar to that of the former, healthier, donor population [12].

After kidney donation, renal hemodynamic reserve capacity is decreased [13-15], most likely resulting from a state of renal vasodilatation that occurs in the remaining kidney as part of the compensatory response [13]. It is unknown whether renal reserve capacity after kidney donation is affected by risk factors for renal function loss, such as older age and higher body mass index.

Based on the above studies, we hypothesized that the decrease in renal reserve capacity after kidney donation would be larger in older and in overweight subjects. To test this hypothesis, we analysed data on renal reserve before and early after donation in 178 living kidney donors and analysed for the impact of age and BMI.

## Methods

The study population consisted of 178 consecutive living kidney donors (age  $48 \pm 11$  years, 39% male, mean BMI  $25.5 \pm 4.1$  kg/m<sup>2</sup>) who underwent the screening protocol with subsequent donation in the University Medical Center Groningen between 1984 and 2005. All donors were normotensive or with well-regulated blood pressure by maximum of one antihypertensive drug (eight subjects), they did not have a history of diabetes,



**Figure 1. BMI and age related differences in renal reserve capacity.**

Renal reserve capacity is expressed as the percentage rise in GFR after infusion of low-dose dopamine. There were no statistically significant differences in pre-donation reserve capacity between the groups of BMI or age (all ANOVA  $p > 0.10$ ). After donation, reserve capacity was lower in donors with higher BMI and older age: Left panel: post-donation reserve capacity differed between BMI class:  $p = 0.005$  (ANOVA). Post-hoc analyses: overweight vs. normal weight  $p = 0.086$ , overweight vs. obese  $p = 0.046$ . Obese vs. normal weight  $p = 0.002$ . Normal weight:  $n = 87$ ; overweight:  $n = 70$ ; obese:  $n = 21$ . Right panel: post-donation reserve capacity differed between tertiles of age at donation:  $p = 0.006$  (ANOVA). Post-hoc analyses: oldest vs. middle tertile  $p = 0.036$ . Oldest vs. youngest tertile  $p = 0.002$ . Abbreviations; BMI, body mass index; GFR, glomerular filtration rate.

kidney disease or cardiovascular events. Potential donors with latent diabetes, identified by abnormal oral glucose tolerance test, were excluded from donation. Physical examination did not reveal abnormal findings. In our centre, glomerular filtration rate (GFR) and its reserve capacity are routinely measured as part of the living donation protocol. As described below, GFR was measured as the clearance of  $^{125}\text{I}$ -iothalamate, first without stimulation, and directly hereafter during stimulation by low-dose dopamine. Measurements were performed 4 months before and 2 months after kidney donation. All donors consented with the use of their clinical data for study purposes.

### Renal hemodynamic measurements

GFR was measured by combined constant infusion of radio-labeled tracers  $^{125}\text{I}$ -iothalamate and  $^{131}\text{I}$ -hippurate, the

donors being in a quiet room, in the semi-supine position. After drawing a blank blood sample, a priming solution containing 0.04 ml/kg body weight of the infusion solution (0.04 MBq of  $^{125}\text{I}$ -iothalamate and 0.03 MBq of  $^{131}\text{I}$ -hippurate) plus an extra of 0.6 MBq of  $^{125}\text{I}$ -iothalamate was given at 08.00 hours a.m., followed by infusion at 12 ml/h. In order to attain stable plasma concentrations of both tracers, a 2-hour stabilization period followed, after which baseline measurements started at 10.00 hours a.m.. The clearances were calculated as  $(U \cdot V)/P$  and  $(I \cdot V)/P$ , respectively.  $U \cdot V$  represents the urinary excretion of the tracer,  $I \cdot V$  represents the infusion rate of the tracer and  $P$  represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of  $^{125}\text{I}$ -iothalamate

with the ratio of the plasma and urinary clearance of  $^{131}\text{I}$ -hippurate. The day-to-day variability for GFR is 2.5% [16].

To obtain reserve capacity, the above-described baseline procedure was extended for 2 hours. During this period, dopamine was infused at a rate of 1.5  $\mu\text{g}/\text{kg}$  per minute. GFR during these 2 hours was compared with baseline GFR and expressed both as the absolute change in GFR in  $\text{ml}/\text{min}$  and as the percentage change. A clinically relevant adequate reserve response was defined as a rise in GFR to dopamine that exceeded the 2.5% variability of the GFR-assay. Therefore a cut-off of 2  $\text{ml}/\text{min}$  was applied for post-donation renal reserve.

Body mass index (BMI) was calculated as ( $\text{body weight} / \text{length}^2$ ) and divided into classes as follows: normal weight: BMI  $<25 \text{ kg}/\text{m}^2$ , overweight: BMI  $25\text{--}29.9 \text{ kg}/\text{m}^2$ , obesity: BMI  $\geq 30 \text{ kg}/\text{m}^2$ .

### Statistical analysis

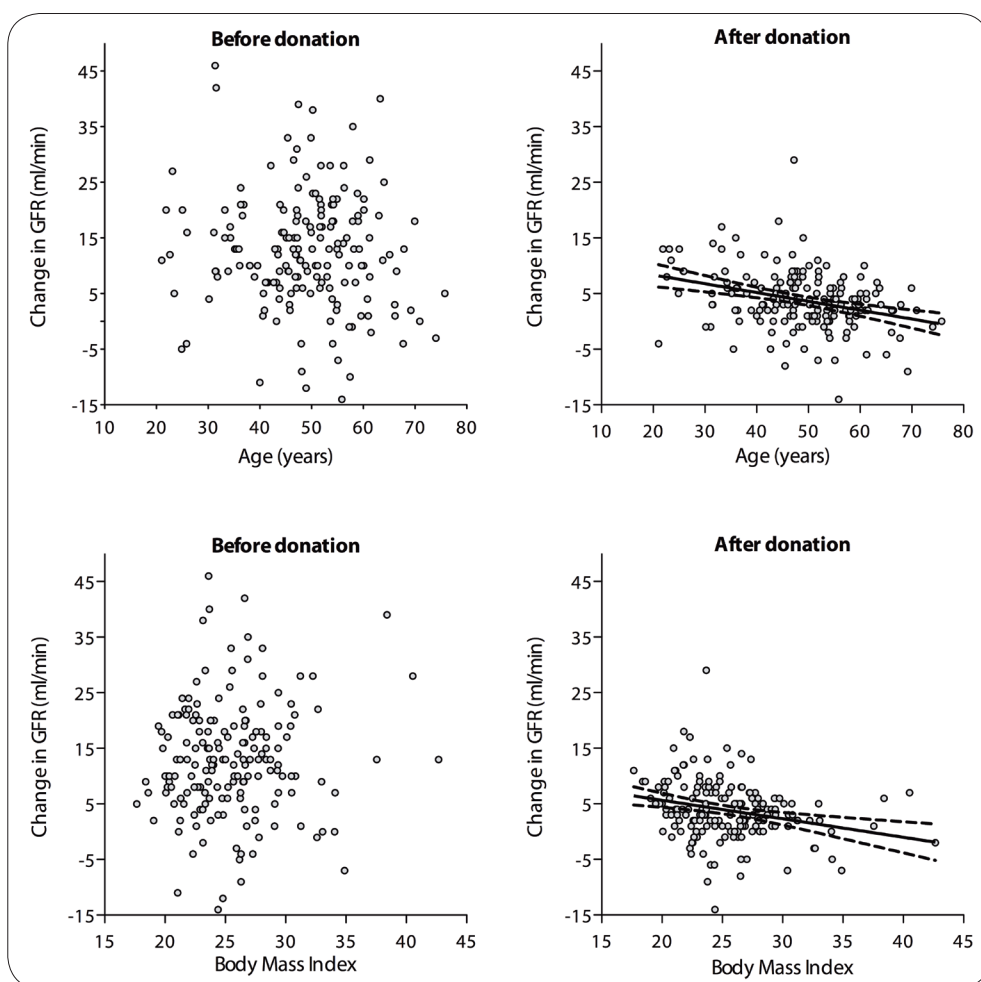
Data are presented as mean  $\pm$  standard deviation unless stated otherwise. GFR data are presented as absolute values ( $\text{ml}/\text{min}$ ) as well as indexed to height ( $\text{ml}/\text{min}/\text{m}$ ). Whereas usually GFR is indexed to BSA, the close association between BSA and BMI has been recognized to introduce bias in analyses of the impact of BMI on renal function [17,18]. Therefore, indexing to height has been recommended. Renal reserve capacity was analysed as the percentage change in GFR and as the absolute change in GFR induced by dopamine infusion. Associations were analysed by univariate analysis (Pearson). In addition, multi-linear regression analysis was applied with age and BMI as independent variables entered into the regression equation and renal hemodynamic parameters (proportional rise in GFR) as dependent variables. Influence of donor age on renal function

and reserve was assessed by age as a continuous variable as well as by tertiles of age. Differences in reserve capacity between BMI classes were analysed by analysis of variance (ANOVA) followed by post-hoc analysis (LSD) to account for multiple comparisons. Furthermore, we applied ANOVA and post-hoc analyses to reserve capacity in the different tertiles of age. The above-mentioned cut-off of 2  $\text{ml}/\text{min}$  change in GFR in response to dopamine was adapted in logistic regression and ROC analyses to predict adequate reserve capacity from either age or BMI. To account for possible interaction between BMI and age, the interaction term was calculated as (BMI \* age), and analysed as a continuous variable. Finally, ANOVA and general linear modelling were applied to the combination of BMI and age. Statistical analyses were performed by using SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

## Results

### Characteristics; renal function and renal reserve

39% of donors were male. Mean donor age was  $48 \pm 11$  years and mean BMI was  $25.5 \pm 4.1 \text{ kg}/\text{m}^2$ . Before kidney donation, baseline GFR was  $114 \pm 20 \text{ ml}/\text{min}$ , with a reduction to  $64 \pm 7\%$  of pre-donation values after donation ( $p \leq 0.001$ ). Before donation, infusion of low-dose dopamine (GFR<sub>dopa</sub>) significantly increased GFR to  $126 \pm 24 \text{ ml}/\text{min}$ ,  $p \leq 0.001$  versus baseline. After donation, infusion of low-dose dopamine induced an increase in GFR from  $72 \pm 12 \text{ ml}/\text{min}$  to  $76 \pm 13 \text{ ml}/\text{min}$  ( $p \leq 0.001$  versus post-donation baseline values). Post-donation renal reserve was significantly reduced compared to pre-donation renal reserve ( $p \leq 0.001$ ).



**Figure 2. Renal reserve capacity in relation to BMI and age before and after kidney donation.**

Renal reserve capacity is expressed as delta GFR (absolute change in GFR after constant infusion of low-dose dopamine). Lines represent regression with 95% confidence interval of the mean. Before donation, renal reserve did not correlate to age or BMI. After donation, higher BMI ( $R=-0.26$ ;  $p\leq 0.001$ ) and older age ( $R=-0.33$ ;  $p\leq 0.001$ ) were negatively associated with renal reserve.

The population characteristics are given in table 1 for break up by BMI class. Of the whole population, more than half were either overweight (70/178) or obese (21/178). Pre-donation uncorrected GFR was highest in the higher BMI classes, albeit only of borderline statistical significance. Height-corrected, GFR was significantly higher in donors with overweight and obesity (also table 1).

There were no differences in pre-donation reserve capacity between the different classes of BMI. Remarkably, post-donation reserve capacity was significantly different between the different BMI classes, with a lower RC in overweight and obese subjects, both when expressed as ml/min and as % change, shown in the upper panel of figure 1. In obese subjects, the response to dopamine did no longer



reach statistical significance, indicating lack of post-donation reserve capacity.

Table 2 shows population characteristics for break-up by tertiles of age. As anticipated, both absolute GFR and height-corrected GFR were significantly lower in older subjects, before as well as after donation. Before donation, reserve capacity was not different for the age groups. After donation, however, reserve capacity was significantly lower in the older age groups, both when expressed as ml/min change and as % change, which is shown in the right panel of figure 1. Yet, even in the oldest age category, there was still a significant post-donation response to dopamine.

### **Determinants of renal reserve: univariate analysis**

To exclude a possible confounding effect of the categorization of BMI and age, respectively, we also analysed BMI and age as continuous variables in determining renal reserve. Scatter-plots for the relation between the response of GFR to dopamine and BMI and age, respectively, are shown in figure 2. The left panels show data before donation and the right panels show data after donation. Before donation, the renal responses to dopamine did not correlate to BMI or to age. After donation, however, the change in GFR to dopamine correlated negatively with BMI and age, both when expressed as a percentage (for BMI:  $R=-0.26$ , for age  $R=-0.28$ ; both  $p\leq 0.001$ ) and when expressed as ml/min (for BMI:  $R=-0.28$ , for age  $R=-0.33$ ; both  $p\leq 0.001$ ).

### **Combined effect of BMI and age on post-donation RC**

Older age and higher BMI are usually associated with one another so it is relevant to investigate both their independent and their combined effects.

As anticipated, in our population, age positively correlated to BMI ( $R=0.19$ ,  $p\leq 0.01$ ). To test whether the effects of BMI and age on post-donation reserve capacity were independent, first, we performed partial univariate correlation analyses. In these analyses, BMI when corrected for age, and age when corrected for BMI, were still negatively and significantly associated with reserve capacity ( $p\leq 0.001$  and  $p=0.008$ , respectively). Second, on multivariate analysis, both age ( $p\leq 0.001$ ) and BMI ( $p=0.003$ ) were independent negative predictors of the overall GFR response to dopamine ( $R^2$  of 0.13;  $p\leq 0.001$ ).

General linear modelling was performed to substantiate and visualize the presence of interaction between BMI and age for post-donation reserve. In this model, we found a significant interaction between BMI and age ( $R^2=0.17$ ,  $p\leq 0.001$ ), with BMI in classes and age in tertiles (in line with the data presentation in **tables 1 and 2**). The top panel of **figure 3** shows the effect of overweight or obesity on renal reserve capacity by age group (with, for graphical clarity, data provided by cut-off at median age, ANOVA  $p=0.002$ ). There was a statistically significant difference in RC between younger and older donors with normal weight (post-hoc  $p=0.005$ ). However, when overweight or obesity was present, there was no longer a difference between younger and older donors ( $p=0.116$  and  $p=0.594$ , respectively).

### **Determinants of the post-donation decrease in RC**

As shown in **tables 1 and 2**, reserve capacity was significantly reduced after donation. To identify the determinants of the decrease in reserve capacity, we performed both univariate and multivariate analyses on the decrease in renal reserve, obtained as pre-donation RC minus post-donation RC (ml/min). On univariate



	Normal (n=87)	Overweight (n=70)	Obese (n=21)	p-value (ANOVA)
<b>Before donation</b>				
Age (years)	46±11	49±11	52±8	0.07
Body mass index (kg/m <sup>2</sup> )	22.4±1.7	27.0±1.4	33.5±3.7	<i>by default</i>
Percentage male donors	34%	47%	33%	NS
GFR baseline (ml/min)	111±15	117±23	119±24	0.07
GFR <sub>dopa</sub> (ml/min)	122±19*	129±28*	132±27*	0.10
Absolute change in GFR to dopamine	11.7±9.9	12.4±13.7	12.6±12.8	NS
Percentage change in GFR to dopamine	10.6±8.7	10.8±10.4	11.1±11.9	NS
GFR normalized for height (ml/min/m)	64±8	68±11	70±13	≤0.01
GFR <sub>dopa</sub> normalized for height (ml/min/m)	71±10*	74±14*	78±15*	≤0.05
Serum creatinine (mg/dl) <sup>a</sup>	0.9±0.1	1.0±0.1	0.9±0.1	NS
<b>After donation</b>				
GFR baseline (ml/min)	70±11	74±13	74±11	0.10
GFR <sub>dopa</sub> (ml/min)	75±14*	77±13*	76±12	NS
Absolute change in GFR to dopamine	4.9±6.1	3.4±4.1	0.9±4.0	≤0.01
Percentage change in GFR to dopamine	6.7±8.4	4.8±5.5	1.3±5.5	≤0.01
GFR normalized for height (ml/min/m)	41±6	42±6	45±6	≤0.01
GFR <sub>dopa</sub> normalized for height (ml/min/m)	43±8*	44±7*	45±6	NS
Serum creatinine (mg/dl) <sup>b</sup>	1.3±0.2	1.4±0.2	1.3±0.2	≤0.01

**Table 1. Descriptive statistics before and after donation for different classes of BMI.**

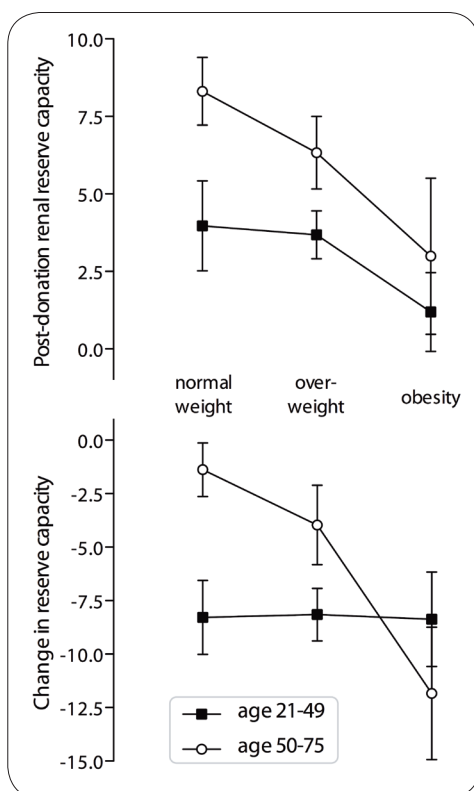
Data are provided as mean ± standard deviation; normal weight: BMI <25, overweight: BMI 25-29.9, obese: BMI ≥30. ANOVA was used to test the differences between the weight classes. Creatinine converted from mg/dl into μmol/l: <sup>a</sup> before donation, normal weight 83±11 μmol/l; overweight 86±13 μmol/l; obese 80±11 μmol/l; <sup>b</sup> after donation, normal weight 111±17 μmol/l; overweight 120±19 μmol/l; obese donors 115±20 μmol/l. Abbreviations: BMI, body mass index; GFR<sub>dopa</sub>, GFR after infusion of low-dose dopamine; GFR, glomerular filtration rate; ANOVA, analysis of variance. \* Dopamine-stimulated GFR values compared to baseline values: p<0.001, before as well as after donation (paired t-tests). To prevent introduction of bias by body weight, GFR was corrected for height.

	1 <sup>st</sup> tertile (n=62)	2 <sup>nd</sup> tertile (n=59)	3 <sup>rd</sup> tertile (n=57)	p-value (ANOVA)
<b>Before donation</b>				
Age (years, range)	21-45	46-53	54-75	<i>by default</i>
Body mass index (kg/m <sup>2</sup> )	24.3±4.3	25.8±3.9	26.5±4.0	0.01
Percentage male donors	40%	37%	40%	NS
GFR baseline (ml/min)	123±19	113±19	105±17	<0.001
GFR <sub>dopa</sub> (ml/min)	135±23*	127±23*	116±22*	<0.001
Absolute change in GFR to dopamine	11.8±11.9	14.1±10.2	10.4±12.9	NS
Percentage change in GFR to dopamine	9.6±8.9	12.6±8.9	10.1±11.2	NS
GFR normalized for height (ml/min/m)	71±9	65±9	61±9	<0.001
GFR <sub>dopa</sub> normalized for height (ml/min/m)	78±12*	73±12*	67±12*	<0.001
Serum creatinine (mg/dl) <sup>a</sup>	0.9±0.1	0.9±0.1	1.0±0.2	NS
<b>After donation</b>				
GFR (ml/min)	77±10	72±12	66±10	<0.001
GFR <sub>dopa</sub> (ml/min)	83±11*	77±13*	68±11*	<0.001
Absolute change in GFR to dopamine	5.3±5.5	4.4±5.5	1.8±4.2	0.001
Percentage change in GFR to dopamine	7.1±7.3	6.1±7.2	2.8±6.1	0.002
GFR normalized for height (ml/min/m)	44±6	42±6	39±6	<0.001
GFR <sub>dopa</sub> normalized for height (ml/min/m)	48±6*	44±7*	40±6 <sup>#</sup>	<0.001
Serum creatinine (mg/dl) <sup>b</sup>	1.3±0.2	1.3±0.2	1.3±0.3	0.09

**Table 2. Descriptive statistics before and after living kidney donation for tertiles of age.**

Data are provided as mean ± standard deviation unless stated otherwise. ANOVA was used to test the differences between the tertiles. Creatinine converted from mg/dl into µmol/l: <sup>a</sup> before donation, first tertile 84±9 µmol/l; second tertile 83±11 µmol/l; third tertile 84±15 µmol/l; <sup>b</sup> after donation, first tertile 112±16 µmol/l; second tertile 114±16 µmol/l; third tertile 119±23 µmol/l. Dopamine-stimulated GFR values compared to baseline values:

\* p<0.001, before as well as after donation, <sup>#</sup> p<0.05 (paired t-tests). Abbreviations: GFR, glomerular filtration rate; ANOVA, analysis of variance.



**Figure 3. Age and BMI interact in the post-donation loss of renal reserve.**

The donation-induced decrease in reserve capacity is plotted for age below (open circles) or above (black squares) the median of 49 years and different classes of BMI. Upper panel: reserve capacity expressed as renal response to dopamine in terms of a percentage. Lower panel: change in reserve capacity obtained as post-donation RC minus pre-donation RC. Younger donors (<49) with normal weight (BMI <25) had a statistical significant smaller decrease in reserve capacity compared to older donors with normal weight ( $p=0.005$ ; post-hoc analysis). However, when overweight (BMI 25–30) or obesity (BMI  $\geq 30$ ) was present, there was no longer a difference between younger or older donors. Furthermore, for younger donors, loss of renal reserve was profound when obesity was present ( $p=0.023$  obese versus normal weight donors with age below the median; post-hoc analysis). For older donors, body mass index did not influence the degree of loss of renal reserve.

analysis, both BMI ( $R=-0.22$ ,  $p=0.003$ ) and age ( $R=-0.20$ ,  $p=0.006$ ) were negatively correlated to the change in renal reserve capacity. Univariate, the interaction term BMI\*age correlated to the decrease in RC ( $R=0.26$ ,  $p\leq 0.001$ ). Multivariate regression analysis showed both factors to be independent determinants of the decrease in reserve capacity. On general linear modelling –entering BMI in classes and age in tertiles– the interaction term was a significant independent variable in predicting post-donation renal reserve capacity ( $R^2=0.14$ ), with a  $p$ -value of 0.002, as illustrated in the lower panel of **figure 3**, which shows by a break-up by median age for graphical clarity that BMI has considerable impact on the decline in reserve capacity in younger, but not older, donors: the nephrectomy-induced loss of renal reserve was most severe for young donors with obesity.

### Prediction of adequate renal response to dopamine

A threshold of 2 ml/min was applied to define adequate renal response. Before donation, renal response to dopamine was below this cut-off for twenty donors. Pre-donation, logistic regression analysis for prediction of inadequate reserve provided a model of borderline significance only (Nagelkerke  $R^2=0.05$ ;  $p=0.08$ ), in which only age was a statistically significant contributor ( $p\leq 0.05$ ). After donation, renal response of 74 donors remained below 2 ml/min. The predicted potential for this inadequate response increased; Nagelkerke  $R^2=0.14$  ( $p\leq 0.01$ ) and both BMI ( $p=0.012$ ) and age ( $p=0.011$ ) contributed to the model. **Figure 4** shows prediction of post-donation renal response to dopamine by BMI and age as ROC curve.

### Analysis of donors with hypertension

Eight donors were using antihypertensive drugs (50% male), three of whom used

ACEi or ARB. Mean age was  $56 \pm 5$  years (range 48-63), versus  $48 \pm 11$  years in the normotensive group (borderline statistical significance of  $p=0.06$ ). Mean BMI was  $28 \pm 3$  kg/m<sup>2</sup> (range 24-31), versus  $25 \pm 4$  kg/m<sup>2</sup> in the normotensive group ( $p=0.15$ ). GFR before and after donor nephrectomy was similar between normotensive and hypertensive donors. Renal reserve capacity was also similar in both groups, before as well as after donation.

## Discussion

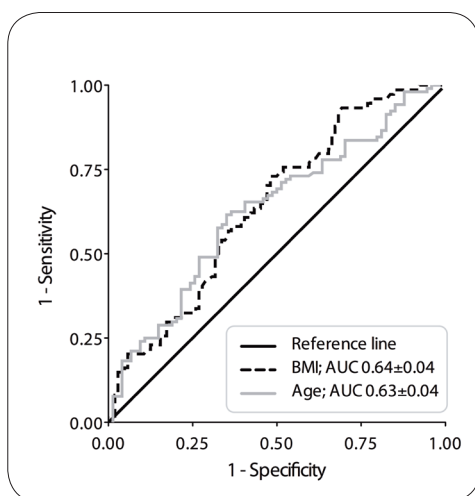
This study, the largest so far on renal reserve capacity before and after living kidney donation, shows that after kidney donation, older age and higher BMI were independently associated with a lower reserve capacity, whereas this was not the case in the same subjects prior to donation.

Renal reserve capacity after kidney donation has been studied in several prior, smaller studies [13-15,19,20]. All studies document presence of reserve capacity after donation. Comparable to our results, renal reserve capacity tested with dopamine was found to be almost halved in kidney donors [13,14,19]. This has been interpreted as a reflection of compensatory hyperperfusion and hyperfiltration of the remaining kidney. There is sparse data to suggest an association between impairment of reserve capacity and the risk for renal function loss. In diabetic patients, loss of renal reserve was found to accompany or precede microalbuminuria and glomerular lesions, well before presence of overt diabetic nephropathy [21-23]. In our study, renal reserve after donation was negatively affected by age and BMI. Moreover, post-donation reserve capacity was completely annihilated in obese donors. It should be mentioned that the post-donation differences in renal

reserve observed here are quantitatively subtle. Based on our current data, it is not warranted to conclude on their clinical significance. However, previous studies have shown that even subtle changes in renal hemodynamics, be it in GFR or filtration fraction, can have prognostic impact for long-term renal function [24,25]. Long-term follow-up, therefore, is warranted to investigate whether the BMI- or age-related impairment or absence of renal reserve after donor nephrectomy is prognostic for an increased risk for renal function loss.

Currently, there is no validated reference value for an adequate renal hemodynamic reserve capacity, neither in subjects with two kidneys nor in subjects with a single kidney. From a clinical point of view, the most relevant definition would perhaps be the amount of renal reserve that allows maintenance of long-term renal function despite uninephrectomy. We cannot ascertain such a cut-off from our current data. However, our data provide a basis to establish the prognostic value of specific cut-offs for reserve capacity in the future, as we provide the largest series on post-donation reserve capacity so far and follow-up studies are ongoing.

Prior studies have reported a decrease in reserve capacity in older subjects, albeit not invariably so [5,9,10]. In our large population, we did not detect an effect of age on reserve capacity prior to kidney donation. This may be due to the fact that kidney donors represent an above-average healthy subset of the population, in whom GFR was also relatively well-preserved with age, albeit lower than in younger subjects. Remarkably, donor nephrectomy elicited an age-related effect on renal reserve capacity. Effects of age on renal reserve have been attributed to impaired vasodilator response due to arteriosclerosis in the kidney's interlobular



**Figure 4. ROC curve for post-donation renal reserve, predicted by age and BMI.**

Presence of post-donation renal reserve was defined at a threshold of 2 mL/min increase in GFR compared to baseline. 74 donors did not reach this threshold after donation. Both BMI and age were independent predictors of adequate renal response on logistic regression analysis. The AUCs are significantly higher than the reference line, for age  $p=0.003$  and for BMI  $p=0.001$ . Abbreviations: AUC, area under the curve; BMI, body mass index.

and arcuate arteries [7]. Apparently, in our older subjects, the condition of the renal vasculature allowed for an appropriate response to dopamine before donation. After donation, due to compensatory vasodilation elicited by the nephrectomy, further vasodilation capacity may have been limited as a possible mechanism underlying the effect of age on renal reserve.

As to the effect of BMI, one prior study documented a reduced reserve capacity in obese hypertensives compared to lean hypertensives [8]. Our study is the first to document an adverse effect of BMI on reserve capacity in normotensive subjects. Again, this effect was not present before donation, but was elicited

by donor nephrectomy. In our study, with a small number of hypertensive subjects, the decrease in renal reserve could not be attributed to hypertension, but the power to detect such an effect was obviously low. Higher BMI was associated with higher baseline GFR, which may be a reflection of hyperfiltration due to weight excess, thus compromising renal reserve. Nevertheless, it is remarkable that before donation, apparently the higher baseline GFR in the same subjects did not result in a detectably lower reserve capacity. It would be logical to assume that the reduction in renal mass calls on the renal reserve to maintain overall GFR, that weight excess-associated hyperfiltration calls on renal reserve by a similar mechanism and that their combination thus resulted in the observed decrease in renal reserve capacity.

Previously, we found both higher BMI and age to be associated with the magnitude of renal function loss after kidney donation [11]. Our current data demonstrate that these same factors are associated with reduced post-donation renal reserve capacity. Since higher BMI has in particular been associated with higher risk for renal damage after nephrectomy [26], our findings of a reduced post-donation renal reserve in kidney donors with higher BMI may be of clinical relevance. The higher baseline GFR in these donors may explain loss of post-donation adequate reserve capacity due to weight-excess related hyperfiltration. In this respect, it is relevant to note that weight loss has been shown to correct obesity induced hyperfiltration [27], so a potentially favourable intervention is available.

Remarkably, we observed that presence of overweight had more impact on loss of reserve capacity in younger donors. Younger donors with overweight or obesity displayed a loss of renal reserve

that was similar to the loss of reserve of older donors, in whom it occurred irrespective of BMI. Moreover, in obese donors, the capacity to increase GFR to low-dose dopamine was annihilated after donation. Our current study design, with only a brief duration of follow-up after donation, does not allow to substantiate the clinical significance of this finding. Theoretically, absence of reserve capacity might be an unfavourable prognostic sign, indicating glomerular hyperfiltration, which could be harmful in the long run.

Our study has several limitations. First, we have only one time-point after donation, which was on a relatively short-term. Moreover, it is uncertain how long-term adaptive responses could further modulate reserve capacity and it is unknown whether overweight or older donors adapt to nephrectomy over a different time-frame. Second, our study was performed in a predominantly Caucasian population, which limits the generalizability of our data. There is some evidence that ethnic factors are relevant to renal reserve

capacity and its association with renal damage [23]. Third, the response to dopamine may not represent the maximal vasodilator response of the kidney and thus provide an incomplete assessment of renal reserve. Finally, as noted above, the clinical and prognostic impact of renal reserve, and changes in renal reserve, have not convincingly been established. Long-term follow-up studies are therefore needed to establish the clinical impact of our findings.

In conclusion, weight excess and older age are associated with impairment of post-donation renal reserve capacity. We emphasize the need for donor follow-up especially when obesity is involved in younger donors, since these donors are potentially exposed to an increased renal risk for a long period of time. Though a potential benefit from weight loss, low protein diet and/or ACE inhibition remains to be investigated, weight loss should be emphasized in donors with excess body weight.

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